

# A physical model for dementia

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Aging associated brain decline often result in some kind of dementia. Even when this is a complex brain disorder a physical model can be used in order to describe its general behavior. This model is based in first principles. A probabilistic model for the development of dementia is obtained and fitted to some experimental data obtained from the Alzheimer's Disease Neuroimaging Initiative. It is explained how dementia appears as a consequence of aging and why it is irreversible.

## I. INTRODUCTION

Dementia is a decline in mental ability, caused by damage to brain cells, that interferes with daily life. Activities of daily living are usually divided into basic and instrumental activities of daily living (IADL) [1, 2].

Several criteria and methods have been developed as measuring tools to implement treatments and diagnoses [3–6]. Despite the efforts developed in this field, the relationship between IADL performance and mental activity is nowadays implemented using only simple statistical approaches like Pearson's or Spearman's correlations.

On the other hand, catastrophe theory, particularly cusp catastrophe models, have been used to describe several psychological processes and human activities (drinking, sexual interactions, nursing turnover, etc) [7–20]. However, in those studies, the data were fit to a cusp surface without support from any phenomenological model, so that the physical reasons of those processes remain obscure. Here, we introduce a physical representation of brain functions representing the brain tasks as creation of networks between several neurons.

## II. THEORETICAL MODEL

In order to support a brain task, a network between several neurons is created. This network is characterized by a correlation length,  $x$ , [21] that depends both on the topology and on the functionality of the network [22]. The degree of metabolic activity necessary to support the task (and the network) is proportional to the volume of the network determined by this correlation length. This metabolic activity is equal to the energy used to maintain the function of the neurons and their links,  $m_0$ , plus the energy required for the dynamic formation of the specific network,  $m_x$ .

However each brain task is not instantiated in its own isolated network. Networks are shared between tasks resulting in connectivity hubs [23]. When several cognitive processes share the same network, they may do so without a proportional increase in metabolic demand. In order to characterize this phenomenon, we introduce the concept of synaptic overlap. The degree of synaptic overlap is proportional to the mean shared area, which is energized by other processes along the network's correlation length. This characteristic network overlap has been well described and is often referred to as a network of networks [21].

So, the energetic balance of the network is summarized as,

$$m_x + m_0 = ax^3 - bx^2, \quad (1)$$

where  $a$  and  $b$  are coefficients that convert the geometric characterization of the network into energy units and

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\* Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: [http://adni.loni.usc.edu/wp-content/uploads/how\\_to\\_apply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf)

$r$  characterizes the synaptic overlap. Equation (1) describes the possible values of the system in the space determined by metabolic energy, synaptic overlap, and correlation length  $(m_x, r^2, x)$ .

Since neuronal network set up is a synchronized response to an electrical stimulus [24] it seems reasonable that a faster network configuration involves more energy. Let us now assume that the metabolic energy for a cognitive task is proportional to the change rate of the correlation length between neurons, that is,  $m_x \sim dx/dt$ . So, equation (1) could be written as,

$$\frac{dx}{dt} = x^3 - \beta x - \alpha = \frac{\partial U}{\partial x}, \quad (2)$$

where now  $\alpha$  and  $\beta$  are functions derived from equation (1) that depend, in general, on metabolic energy, synaptic overlap and time, and where  $U$  is a potential function that corresponds to the Riemann-Hugoniot surface  $x^3 - \beta x - \alpha = 0$  for different  $\alpha$  and  $\beta$  values. Equation (2), or the equivalent potential, describes a cusp model [25, 26] that predicts sudden changes for  $x$  values; here  $\alpha$  and  $\beta$  are known as asymmetry control parameter and bifurcation control parameter respectively.

Equation (2) is thus a deterministic model that relates the energy in a cognitive task network to its correlation length. However, the brain networks are subject to a high level of noise [24]. The coupling of millions of neurons in a network in order to do a task is necessarily subject to random variations. In order to apply this model to real data a probabilistic term should be added to the model.

This casts equation (2) into a stochastic differential equation,

$$\frac{dx}{dt} = \frac{\partial U}{\partial x} + \sigma(x) W(t), \quad (3)$$

where  $\sigma(x)$  represents a diffusion process, that will be assumed to be constant, and which  $W(t)$  is a white noise Wiener process. Notice that (3) is a Langevin equation where the correlation length corresponds to the position of the particle under the potential. The corresponding Fokker-Planck equation for the probability density can be written as,

$$\frac{\partial \rho(x, t)}{\partial t} = \frac{\partial}{\partial x} \left[ \frac{\partial U(x)}{\partial x} \rho(x, t) \right] + \sigma \frac{\partial^2}{\partial x^2} \rho(x, t). \quad (4)$$

Nevertheless, equation (4) involves two different characteristic times. Changes in  $x$  occur in the time of task processing and brain network assembling, that is, in seconds or minutes. Alterations of  $U$ , and consequently of  $\rho$ , are due to the development of the neurodegenerative diseases that act in a time scale of years. Since the variation of  $x$  in time is faster than the change of  $U$ , it can be assumed that  $\rho$  changes very slowly over time, and consequently  $\partial \rho / \partial t \simeq 0$ .

From this, it is straightforward that,

$$\rho(x) = C e^{-[\frac{1}{4}x^4 - \frac{1}{2}\beta x^2 - \alpha x]}, \quad (5)$$

where  $C$  is a normalization constant.

This last expression gives the probability density of obtaining a network of size  $x$  for the steady state case, that is, if the system varies slowly over time.

Since the probability density for a network with correlation length  $x$  is known, the entropy of the set of networks, can be calculated as,

$$S(\alpha, \beta) = - \int_0^\infty \rho(y) \ln(\rho(y)) dy, \quad (6)$$

showing the natural evolution of the system.

### III. DATA FITTING

In order to evaluate our model we fit some real data. We should determine first how to model the correlation length of the network. On one hand, neurodegenerative diseases affect first the largest networks [27] and this is reflected in the impairment of the more complex task.

On the other hand, we should consider the evolution of the brain. From one organism to other, brain has growth in size and complexity. While the new evolved life forms are able to learn more complex task, their brain grow in new layers and connected networks [28].

Notice also that high frequency activity in brain has been associated to cognitive process [29] implying that high functioning requires more energy.

So, the correlation length of the network will be modeled as proportional to the network output. That is, a bigger network is assumed as needed in order to accomplish a more difficult task.

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

ADNI is a global research effort devote to the research of AD. The website group clinical, imaging, genetic and biospecimen biomarkers from normal aging to dementia stages. The standardized methods for imaging and biomarker collection and analysis are intended for facilitating a cohesive research worldwide. ADNI provides the collected information to all registered members.

A sample of 1351 subjects was selected from ADNI cohort. All available data from these individuals gave a total of 3025 study visits. We selected for analysis: positron emission tomography fluorodeoxyglucose (FDG) standard uptake value ratio, total brain volume (TBV), intracranial volume (ICV), as well as the functional activities questionnaire (FAQ) score. This questionnaire is the information obtained from caregivers about IADL

performance of patients. For each subject the brain ratio (BR) was calculated as the ratio between TBV and ICV.

For each variable to be fitted into the model, FDG, BR and FAQ, a linear transformation was applied to the data in order to normalize it to the interval  $[0, 1]$ . In the case of FAQ values the transformation was applied in opposite direction. That is, the FAQ score increases as impairment of IADL increases but the normalized variable decreases as impairment of IADL increases.

The network output is proposed as proportional to IADL; the bifurcation ( $\beta$ ) and asymmetry ( $\alpha$ ) control parameters are proposed as linear functions of the independent variables [30]. That is,

$$\begin{aligned} x &= w_0 + w_1 f \\ \alpha &= a_0 + a_1 u + a_2 v, \\ \beta &= b_0 + b_1 u + b_2 v \end{aligned} \quad (7)$$

where  $f$ ,  $u$  and  $v$  stand for the normalized values of FAQ, FDG and BR and  $w_i$ ,  $a_i$  and  $b_i$  are fitting coefficients.

All the statistical procedures were made using R Statistical Software [31]. The R package “cusp” calculate the Cobb’s pseudo- $R^2$  parameter as a measurement of the goodness of fit [30]. Cobb’s pseudo- $R^2$  and Pearson’s  $R^2$  corresponding to the linear model  $x = c_0 + c_1 f + c_2 u + c_3 v$  were calculated and compared each other. The software fits the data to the *standard* cusp model, where the bifurcation is centered at  $\alpha = 0$ ,  $\beta = 0$  and  $x = 0$ . However, by requiring to (7) that  $w_0 = a_0 = b_0 = 0$ , as boundary conditions, the data were fitted to (3).

#### IV. RESULTS

The Cobb’s correlation coefficient for the ADNI data was pseudo- $R^2 = 0.68$  that seems to be a much better fit compared to the Pearson’s correlation coefficient  $R^2 = 0.35$  of the equivalent linear model. Fitting coefficients of the Riemann-Hugoniot surface on  $(\alpha, \beta, x)$  space were  $w_1 = 4.6$ ,  $a_1 = 6.6$ ,  $a_2 = 5.4$ ,  $b_1 = 2.8$  and  $b_2 = 0.1$ .

Figure 1 shows the control plane of the cusp model and how the data distribute for  $\alpha$  and  $\beta$  values. It can be seen that there is a preferential direction along the cusp surface, represented as a straight line. By translating and rotating the coordinate system, so that  $\alpha$  lies over this straight line and applying the boundary conditions,  $x$  can be expressed in its “natural” coordinate system  $(\alpha', \beta')$ . Figure 2 is the representation of the data in the new coordinate system. It shows how the data distribute for  $x$  values. Here, it can be seen that two different results are possible, IADL task failure for low values of IADL performance, and success, for high values of IADL performance.

#### V. DISCUSSION

The entropy of the system, calculated according to (6) and represented in Figure 3, defines the possible evolu-

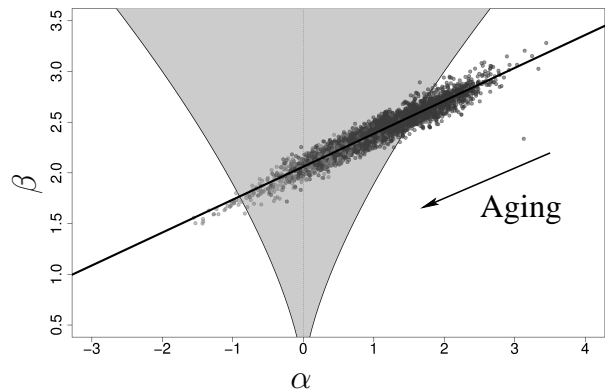


Figure 1. Control surface of the cusp model. Shaded area represents the bivaluated zone of the cusp. The straight line represents the most probable trajectory on the plane. Arrow shows the general direction of aging. Darkness of points is proportional to the value of the correlation length.

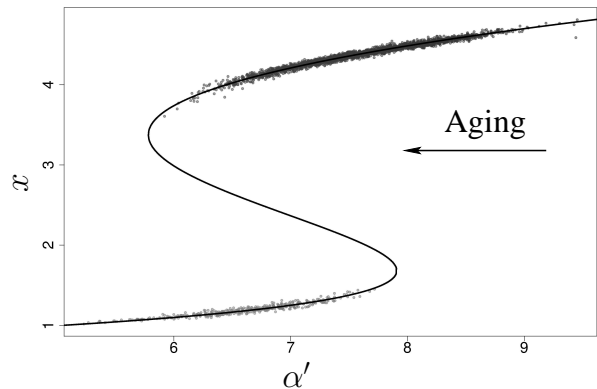


Figure 2. Change of possible values of the network correlation length along the most probable trajectory represented by  $\alpha'$  line. The arrow shows the direction of aging. Darkness of points is proportional to the value of the correlation length.

tion of the system in time. The system evolves in the general direction of the known aging processes of brain, represented with arrows in Figures 1 and 2. However, the maximum value of entropy corresponds to the point of  $\alpha = 0$  and  $\beta \simeq 2.15$ , very close to the point where the data intersects the  $\alpha = 0$  plane ( $\beta = 2.06$ ).

Older age is generally characterized by decreasing brain volume [32] and a decline in brain glucose metabolism [33–35]. Our model shows that even if this declining process occurs slowly it could end in a catastrophic failures of IADL, that is, in dementia. Even when older individuals are more likely to present multiple pathologies [36] it has been observed that some very old people get dementia without the presence of any pathology. That is, even when age is associated to pathological processes a non small percentage of the oldest people get

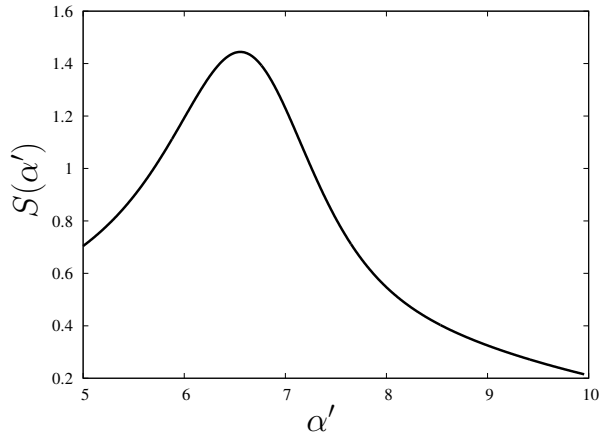


Figure 3. Entropy of the system as a function of  $\alpha'$ . The maximum value of entropy is for  $\alpha' \simeq 6.5$ .

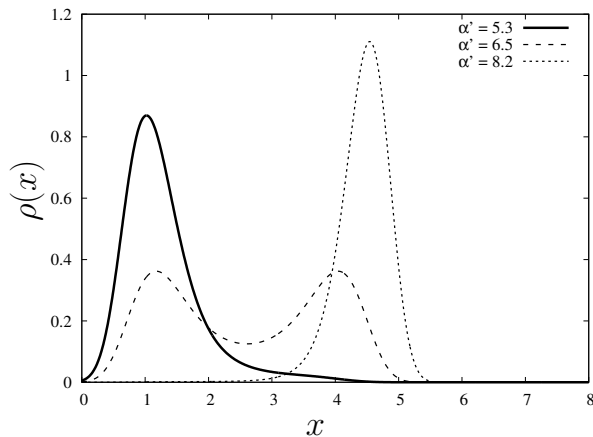


Figure 4. Probability density of obtaining a network of size  $x$  for different values of  $\alpha'$  along the most probable evolution of the system.

dementia without any pathology [37].

As can be seen in Figure 4, the "high energy" states produce only networks with high output. However, when there is a loss of brain volume with older age and a lower energy use, a point is reached where the probability of producing a network with a very low output is not zero. That is, the probability of task failure suddenly becomes greater than zero. This probability of failure increases along the aging process while the probability of success decreases. At some point along this continuum, an individual will be diagnosed with dementia. At very low values of BR and FDG the probability of success will be zero.

Our results show that functional brain decline is clearly observed through the measures of the energy consumption (FDG) and the brain volume (BR). Dementia progression has been already associated with the lesser presence of brain energy consumption [38]. Furthermore, it

has been observed that the decline in energy consumption increases in advanced disease stages [39] pointing to a non linear relation between both magnitudes. Other authors have linked the IADL impairment to brain atrophy [1, 40] and also abrupt changes of IADL for different levels of brain atrophy have been observed [2], very similar to those changes that our model predicts.

However, there is no deterministic relation between those biomarkers and the onset of dementia. On the contrary, an individual's decline could follow a random path through the surface determined by Equation (2). Furthermore, the precise moment when the subject falls into dementia can not be predicted because it is governed by a probability function.

Beyond statistical inference or linear relationships, a few mathematical models link the brain functioning with observed measures. However, these models are mainly focused into capturing the patterns of the disease instead of offering a general dynamics of the subject impairment progression [41–43].

Here we offer a general framework that can be used to test the weight of clinical variables over the disease. Role of pathological variables could be easily determined by rewriting  $\alpha$  and  $\beta$  expression in equations (7). The influence of comorbidities or other factors usually used as covariables as age or genetic factors could be tested the same way. Fitting coefficients should show if these variables need to be taken into account. For instance, it is clear that in equations (7) the brain atrophy can be neglected from  $\beta$  since the coefficient  $b_2$  is an order of magnitude smaller than the others. However, the inclusion of new variables should modulate the trajectory over the surface described by (2). So, the research over several variables should require much more data in order to show reliable results.

## VI. CONCLUSIONS

It has been argued that dementia is the result of a pathological process acting on the brain and is fundamentally different from what is called healthy aging. However, based on the results of our model, normal aging results in a small, but continuous change in the brain that can drive loss of performance in IADLs. This presents the provocative possibility that at least in some case (e.g., the oldest-old) a dementia syndrome could be an end-point of otherwise normal aging.

However, the solution posed here is only for the steady state. That is, the curve of Figure 2 represents the evolution of system only if changes occur slowly. Stroke, infections, and the like cause abrupt changes to the system, and these are not accounted for in our model. We do not exclude the possibility that dementia could also appear as a consequence of sudden changes on the brain.

While our model explains the general behavior of the data, the entropy of the system, shown in Figure 3 does not explain more advanced cases of dementia. This could



mean that the model should not be applied to the more sparse networks that would be apparent in demented individuals.

This is a novel approach not only in the field of dementia but more generally for neurodegenerative diseases. By applying only first principles of physics, in this case the laws of thermodynamics, we can show how cumulative slow changes in the brain can trigger a catastrophic change in the performance of the functional networks.

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